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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,950	09/30/2005	Timothy P. Tully	21RE-137227	1059

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,950	TULLY ET AL.	
	Examiner	Art Unit	
	ADITI DUTT	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,9,10,12-15,17-22 and 24-30* is/are pending in the application.

4a) Of the above claim(s) *17,18 and 25* is/are withdrawn from consideration.

5)☒ Claim(s) *12-15,19-22 and 24* is/are allowed.

6)☒ Claim(s) *1-4,6,9,10,26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The supplemental amendment filed on 12 January 2011 and the amendment of 10 November 2010 has been entered into the record and has been fully considered. Claims 7 and 8 are cancelled. Claims 1-3, 6 and 9 have been amended. New claims 26-30 have been added.

2. Claims 1-4, 6, 9-10, 12-15, 19-22, 24 and 26-30, drawn to a method of identifying candidate compounds for enhancing CREB pathway function and assessing the effect on CREB-dependent gene expression, are under consideration in the instant application.

3. Claims 17-18, and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 18 February 2008.

Response to Amendment

Withdrawn objections and/or rejections

4. Upon consideration of the cancellation of claims 7 and 8, the rejection under 35 USC § 112, 1st paragraph, scope of enablement is withdrawn.

5. Upon consideration of the cancellation of claims 7 and 8, the rejection of claims under 35 USC § 112, second paragraph is withdrawn.

6. Upon consideration of Applicant's persuasive arguments with respect to the teachings of Shoemaker et al in reference to neuroblastoma cells, the pending rejections under 35 USC § 103(a), are withdrawn.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1 and 3-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ying et al. (JBC 272: 2412-2420, 1997), in view of Tully et al (WO 96/11270, dated 4/18/1996), and in further view of Shastry et al (Intern J. Neurosc 108, 109-126, 2001).

9. The claims are directed to a method of identifying candidate compounds for enhancing CREB pathway function, (i) by contacting host cells comprising an indicator gene linked to a CRE promoter with a test compound and CREB function stimulating

agent (forskolin); (ii) determining the indicator activity and comparing the same in the above cells versus control cells contacted with the CREB function stimulating agent alone; (iii) selecting the test compound if the indicator activity in cells treated with CREB function stimulating agent and test compound is increased relative to the above control cells; (iv) selecting the test compound if the indicator activity in control cells treated with test agent is not significantly different from the activity elicited by control cells not treated with any agent; wherein the host cells are neuroblastoma cell, and the indicator gene is luciferase (claims 1, 3-4).

10. Ying et al. teach that host cells (Calu-6 or human lung cancer cells) were transiently transfected using plasmids comprising the HREN promoter having the consensus CRE sequence (e.g. 900L, 900CRE, etc.) (Table 1; Figure 1), luciferase indicator gene, and expression vector encoding the CREB-1 transcription factor (abstract) and contacted with forskolin (Materials and Methods, page 2413, col 2, para 2). The reference further teaches that the luciferase activity elicited by cells transfected with reporter constructs such as 900CRE, and contacted with CREB expression vector along with forskolin is significantly increased with respect to cells without the CREB expression vector. Additionally, the cells not treated with forskolin and CREB expression vector are not significantly different than cells in contact with CREB expression vector alone (Figure 6A).

Please note that the CREB vector can function as a CREB analog to enhance CREB function, therefore is interpreted as having the same properties of the claimed test compounds.

11. Ying et al. do not teach the screening of a plurality of compounds that would enhance CREB function.

12. Tully et al. teach screening assays of pharmaceutical drugs for enhancing long-term memory by activating CREB or CREB isoforms (page 4, para 4; page 5, para 2), therefore, would inherently include a plurality of compounds.

13. Ying et al. or Tully et al. do not teach using neuroblastoma cells.

14. Shastry et al teach that neuroblastoma cell lines can be transformed and used as a versatile neurobiology model (abstract) and can be used for the screening of various agents, proteins or genes associated with neuronal division, proliferation, differentiation and apoptosis (page 120, para 2; page 119, para 3). The reference also teaches that neuroblastoma cell lines can be used for screening of agents like neurotoxicants (page 114, para 2), and differentiating agents acting via the cyclic AMP (cAMP) pathway (page 118, para 1).

15. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the in vitro CREB activating assay for screening of pharmaceutical agents for enhancing long term memory using non-neuronal cells as taught by Ying et al. and Tully et al., by using neuroblastoma cells, in view of the teachings of Shastry et al. The person of ordinary skill in the art would have been motivated to use neuroblastoma cells and would have expected success because these cells are capable of neuronal differentiation and unlimited proliferation in vitro and therefore, is an excellent in vitro system for various cell based assays in the field of neurobiology and pharmacology.

16. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

17. Claims 1 and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ying et al. (1997), in view of Tully et al (1996), and in further view of Walton et al (Trends Neurosc 23: 48-53, 2000).

18. Claims 9 and 10 recite that the cells of neural origin are hippocampal neuronal cells.

19. The teachings of Ying et al and Tully et al are set forth above.

20. Ying et al. or Tully et al. do not teach using hippocampal neuronal cells for the assay.

21. Walton et al. teaches that CREB regulates many aspects of neuronal functioning and memory formation, and hippocampal neurons expressing CREB induced proteins are selectively vulnerable in neurodegenerative conditions (page 48, col 2, para 2). The reference also teaches that activation of CREB activation occurs in the hippocampal dentate granule cells, and CREB function studies can be done using neurons in vitro (abstract). The reference also teaches that primary neuronal cells have been used for studying CREB gene overexpression (page 52, para 1).

22. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the in vitro CREB activating assay for screening of pharmaceutical agents for enhancing long term memory using non-neuronal cells as taught by Ying et al. and Tully et al., by using neuronal or hippocampal cells, in view of the teachings of Walton et al. The person of ordinary skill in the art would have been motivated to use hippocampal neurons as these cells express CREB, and because CREB protein targeting could be an ideal way to obtain "neuroprotective cognitive enhancement" and thereby develop therapeutics for various neurodegenerative diseases having cognitive or memory impairment, for example Alzheimer's disease

(page 52, last para). The person of ordinary skill in the art would have expected success because in vitro cell based assays using one or more agents were routinely performed in the scientific and medical community, at the time the invention was made.

23. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

24. Claims 1-4, 6, 9, 10 and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ying et al. (1997), and Tully et al. (1996), in view of Shastry et al (2001) and Walton et al (2000), and in further view of Torrance et al (Nature Biotech 19: 942-945, 2001).

25. New claims 26-30 are directed to a method of identifying candidate compounds for enhancing CREB pathway function using host cells wherein selecting the test compound is done if the indicator activity in cells treated with forskolin and test compound is increased $\geq$ 100% relative to the indicator activity in control cells contacted with forskolin only. Claims 2 and 27 recite that the host cells are contacted with the test/candidate compound prior to contact with the CREB function stimulating agent. Claims 6 and 29 recite repeating the method steps with a range of concentrations of the test agent.

26. The teachings of Ying et al, Tully et al, Shastry et al and Walton et al are set forth above.

27. Ying et al., Tully et al. Shastry et al or Walton et al do not teach that the indicator activity in cells treated with forskolin and test compound is increased $\geq$ 100% relative to

the indicator activity in control cells contacted with forskolin only, and repeating the method steps with a range of concentrations of the test agent.

28. Torrance et al teach a standard screening procedure using tumor cells in high-throughput cell-based assays starting with a collection of 29,440 diverse molecules (plurality of compounds) for drug discovery of anticancer therapeutics (abstract; page 945, col 1, para 2 – Experimental protocol (Compounds)). The reference teaches conducting secondary screening with the criteria of a two-fold or greater (i.e. $\geq$ 100%) selectivity of the test compounds identified in the primary stage of selection. Torrance et al teach that the compounds were further tested at a concentration range (eight different concentrations) to determine the optimum concentration eliciting the maximum and a reproducible difference between controls (page 941, para spanning col 1 and 2; Figure 4; page 945, Experimental Protocol – Screening procedure).

29. It would have therefore, been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the in vitro CREB activating assay for screening of pharmaceutical agents for enhancing long term memory using neural host cells as taught by Ying et al., Tully et al., Shastry et al. and Walton et al, by using a screening method in view of Torrance et al. The person of skill would have been motivated to use the screening method of Torrance et al. as it involves standard stages of primary and secondary selection strategies of compounds of interest thereby deriving at a discovery of drugs with stringent selectivity and high specific activity. The person of ordinary skill in the art would have expected success because in vitro cell based assays using one or more agents were routinely performed in the scientific and medical community, at the time the invention was made.

30. Ying et al., Tully et al., Shastry et al. Walton et al. or Torrance et al. do not teach that the host cells are contacted with the test/candidate compound prior to contact with the CREB function stimulating agent.

31. However, since the disclosure does not specify criticality of the claimed time of addition of the test compound, optimization within prior art conditions or through routine experimentation is obvious to one skilled in the art. In the case of contacting the host cell with the test compound prior to forskolin, one of skill in the art would clearly recognize addition of compounds must be timed sufficiently to obtain an optimum activity of the compound. As such, the timing of the addition of the compound in an assay would amount to nothing more than routine experimentation that can be optimized.

As stated in MPEP 2144.05:

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382; Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 UDPQ2d 1843 (Fed. Cir.).*

32. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to determine the optimal time for contacting the test compound with the host cell for optimizing the screening assay and determining a test compound that would enhance the CREB pathway function, in view of the combined teachings of Ying et al., Tully et al., Shastry et al. Walton et al. and Torrance et al. The person of ordinary skill in the art would have been motivated to perform such tests and would have expected success because of the involvement of CREB pathway in multiple biological and cognitive functions.

33. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Applicant's Remarks

34. Applicant traverses the 103 rejections over Ying, Tully and Shoemaker for reasons described below.

(A) Suboptimal dose:

Applicant argues that the cited combination of the above references does not teach or suggest a suboptimal dose of a CREB function stimulation agent (forskolin). Citing the paragraph (pages 19 and 20 of the instant specification) defining suboptimal dose, Applicant asserts that the suboptimal requirement underscores "a guiding principle" "to identify compounds that do not enhance CREB function on their own but rather after co-stimulation with forskolin". Applicant alleges that Ying teachings are deficient and Examiner has not provided a basis that Ying uses suboptimal dose of forskolin. Moreover, Applicant asserts that Ying data indicate the use of optimal amounts of forskolin, primarily because Ying focused on components acting downstream of cAMP. Applicant concludes that the Ying deficiency is not corrected by Tully or Shoemaker.

(B) Neural cells:

Applicant argues that the cited combination of references teaches away from "contacting cells of neural origin". Applicant further argues that Shoemaker et al results teach away from a screening assay using neural cells or neuroblastoma cells.

(C) No teaching of step (g) of claim 1:

Applicant alleges that Examiner's interpretation of Ying results is faulty, because only one data set (900CRE construct in Calu-6 cells) out of 6 constructs in 2 cell lines (figure 6 of Ying) appears to support Examiner's position. Applicant therefore, argues that this

selective reliance "is to the exclusion of all contradictory data in Figure 6" and is therefore, "improper as a matter of law". Directing to current claim amendment, Applicant argues that Ying teaches away from the claimed invention because the "effect of CREB on forskolin induced activity of 900CRE in Calu-6 cells is less that two-fold". Applicant further moves on to Figure 7 of Ying reference, asserting that Calu-6 cells are deficient in cAMP signalling cascade components.

Applicant concludes that because Tully and Shoemaker do not correct the above deficiencies, the rejection should be withdrawn.

Response to Applicant's arguments

35. Please note that all earlier rejections and the Shoemaker reference have been withdrawn. Applicant's current arguments will therefore, be addressed to the extent that those are relevant to the current rejection.

36. (A) Suboptimal dose:

Applicant's arguments are fully considered, however, are not found to be persuasive. Applicant's arguments with regard to downstream effect of cAMP are irrelevant because the effect is still mediated via CREB pathway function as instantly claimed. Applicant's allegation that the downstream action "underscores the need for peak levels of cAMP" is considered, but not found to be persuasive, mainly because the dose of forskolin used in the reference stimulates (induces) CREB pathway function to a level that is above endogenous (basal) levels, such that a further statistically significant increase in CREB pathway function due to induction by a cognitive enhancer can be measured (see instant specification, page 19, para 5, lines 24-26), thereby complying with the suboptimal requirements as stated in the instant specification. For the sake of

argument, even if the concentration of forskolin in Ying is saturating as Applicant contends, the suboptimal concentration can always be determined empirically as stated in the specification (page 20).

37. (B) Neural cells:

Applicant's arguments are fully considered, however, are found to be moot, because the Shoemaker reference is withdrawn and new rejections with new references have been currently provided.

38. (C) No teaching of step (g) of claim 1:

Applicant's arguments are fully considered, however, are not found to be persuasive. Although agreed that there are other constructs and another cell type in the Ying reference, Calu-6 is a host cell and the use of 900CRE in the promoter sequence teaches the invention as claimed. Even though use of the other constructs fails to provide comparable results as the claimed invention, the reference cannot be considered as teaching away. Applicant is reminded that the claims are directed to a screening assay, wherein the preferred requirement is that the compound is selected if the luciferase activity is significantly increased in the presence of forskolin, as demonstrated by the 900CRE construct. Moreover because the 900L and 900MUT are different sequences in the promoter, the comparison cannot be considered as that with equivalents, i.e. involving different promoter sequences and different cell types, which can result in different assay results. Because it is a screening assay involving specific selection criteria, and because 900CRE construct complies with the requirement of step (g) of claim 1, the claimed invention is obvious in view of the combined teachings of the cited references. That other constructs are not showing results as instantly claimed, would therefore, not prove the lack of using "Ying as a whole", because of the above

explained reasons. Applicant's arguments about not considering both cell types in Figure 6 of the Ying paper, is not persuasive, because the instant claims broadly recite "host cells" or "cells of neural origin" (claims 1, 26). Because Ying teaches Calu-6 cells as host cells, and because using the 900CRE construct demonstrates the desired result required in the (g) step of claim 1, the rejection is proper.

39. For reasons explained above, the invention is prima facie obvious over the combined teachings of the references. It is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

40. New claims 26-30:

Applicant argues that even if the 900CRE construct of Ying elicits a significant increase of indicator activity over that of controls, the effect is not $\geq$100% as recited in new claims 26-30.

41. Applicant's arguments are fully considered but not found to be persuasive as it is directed to current claim amendments. Moreover, as stated above it is repeated that the "$\geq$100%" limitation is a routine criteria of selection in high-throughput cell-based drug discovery procedures, which was well-known at the time of filing of the instant invention. Even though Ying does not teach a $\geq$100% (or $\geq$ 2-fold) increased indicator activity over controls, the person of ordinary skill in the art would be motivated to optimize the screening protocol to obtain specific, reproducible and reliable candidate compounds in view of art established screening steps; also corroborated in the instant specification that

states that the "≥ 100%" criteria is set to "exclude statistical positives" before moving to the next screening step (page 37, para 1).

Conclusion

42. Claims 12-15, 19-22 and 24 are allowable.

43. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

44. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

45. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
26 March 2011

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649